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**REMARKS - General**

This is responsive to the Examiner's Office Action mailed May 3, 2007. Applicants have withdrawn claims 1-11 from further consideration; have amended claim 12; have cancelled claims 13-20; and have added new claims 25-26. Thus, claims 12, and 21-26 are pending in this application.

The status of all claims and the text of all pending claims are shown above. In the changes made to the claims by the current amendment, ~~deletions are shown by strikethrough~~, and additions are underlined.

***Discussion of Inventorship***

Applicants certify that the subject matter of the various claims in this patent application was commonly owned at the time any invention covered therein was made absent any evidence to the contrary.

***Discussion of Claim Rejection – 35 USC §112***

1. Claims 12, 15-17, 19 and 21-24 were rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The term "its (genipin) analog, derivatives, and combinations thereof" has been deleted from claim 12 in the claim amendment to overcome claim rejection.

2. Claims 12, 15-17, 19 and 21-24 were rejected because the specification, while being enabling for "therapeutic treatment of restenosis or reduction of intimal smooth muscle cell proliferation following angioplasty", does not reasonably provide enablement for the term "therapeutic treatment". The term "therapeutic treatment" has been deleted from claim 12 in the claim amendment to overcome claim rejection.

3. Claims 12, 15-17, 19 and 21-24 were rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention with the term "consisted of". The term "consisted of" has been deleted from claim 12 in the claim amendment to overcome claim rejection.



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**Discussion of Claims Rejections - 35 USC §103**

Examiner rejected claims 12, 15-17, 19 and 21-24 as being unpatentable over Lin et al. (WO 98/19718) in view of Pinchuk et al. (US 6545097), and further in view of Tsai et al. (Biomaterials 22, 2001, 523-533), Royer (USP 5783214) and Gagnieu et al. (USP 5763579).

Applicants have amended claim 12 to overcome the claim rejection by Examiner with the following reasons:

1. One of the co-inventors of the instant invention, Professor Dr. Hsing-Wen Sung, is a co-author of Lin et al. (WO 98/19718) and Tsai et al. (Biomaterials 22, 2001, 523-533).
2. The amended claim 12 recites genipin-crosslinked pharmaceutical microspheres comprising a gelatin carrier and encapsulated heparin. The claim is further restricted in the dependent claims to (a) oral administration (claim 21), (b) intramuscular administration (claim 22), (c) small microsphere of 20-100  $\mu$ m (claim 23), (d) moderate crosslinkage of about 60% (claim 24), (e) prepared by an emulsification-solvent-extraction method, and (f) manufactured by a spray drying process.
3. Comparison of prior art

	Instant invention (10/622,303)	Lin et al (WO 98/19718)	Pinchuk et al (USP 6545097)
1. microsphere form	YES	no	no
2. oral delivery	YES	no	no
3. gelatin	YES	YES	no
gelatin microsphere	YES	no	no
4. heparin	YES	no	YES
encapsulated heparin	YES	no	no
5. crosslinking-genipin	YES	YES	no
crosslinking~60%	YES	no	no

4. The genipin-crosslinked heparin-encapsulated gelatin microparticle is intended for controlled release of heparin in the body. This controlled release purpose is to avoid overdose shock of acute reaction (due to non-crosslinked microsphere and rapid



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release of heparin) or prolonged underdose (due to highly crosslinked microsphere and delayed release of heparin). None of the cited prior art teaches genipin partially crosslinked heparin-encapsulated gelatin microparticle for intended controlled release of heparin in the body

5. The Lin et al. (WO98/19718) teaches biocompatible implants with tensile strength (such as a pericardium) and high crosslinking having stability toward degradative enzymes. The moderate crosslinking (about 60% partially crosslinked, instead of high crosslinking) of the instant invention as a microsphere drug carrier favors chronic enzymatic digestion; it simultaneously protects the encapsulated heparin within the moderate crosslinked gelatin as shown in the exemplary embodiments.
6. Claims 21-24 are all dependent on the amended independent claim 12. Applicants request re-consideration of claim rejection of claims 12 and 21-24.

### ***Discussion of New Claims***

Applicants have added new dependent claim 25-26 relating to Invention II (claims 12-20) to vary the scope of protection and to protect other features of embodiments of the invention. The new claims are supported by the specification and drawings and no new matter has been introduced. The Examiner's consideration of the new claims is respectfully requested.

For new claims 25 and 26, the claim is supported by example #1 and paragraph [0078] of the instant invention.

### ***Double Patenting***

Claims 12, 15-17 and 21-24 are rejected under the judicially created doctrine of double patenting over claims 7-8, 10-16, 19-20 and 23-29 of U.S. Patent No. 6624138 B1 and further in view of Royer (USP 5783214) and Gagnieu et al. (USP 5763579). A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) is included to overcome an actual or provisional rejection based on a nonstatutory double patenting ground. The conflicting patent (USP 6624138 B1) is commonly owned with this application by the assignee, GP Medical.

### ***Conclusion and Conditional Request For Constructive Assistance***



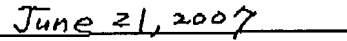
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For all of the above reasons, applicants submit that claims are now in proper form, and that the claims all define patentably over the prior art. Therefore they submit that this application is now in condition for allowance, which action they respectfully solicit. If, for any reason, this application is not believed to be in full condition for allowance, applicants respectfully request the constructive assistance and suggestions of the Examiner pursuant to M.P.E.P. § 706.03(d) and § 707.07(j) in order that the undersigned can place this application in allowable condition as soon as possible and without the need for further proceedings. If further issues remain to be resolved, the Examiner is cordially invited to contact the undersigned (949-887-2966) such that any remaining issues may be promptly resolved.

Respectfully submitted,



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Date